

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 50-756

MICROBIOLOGY REVIEW(S)

HFD-540 White

REVIEW FOR HFD-540

NOV 16 1998

OFFICE OF NEW DRUG CHEMISTRY
MICROBIOLOGY STAFF HFD-805
Microbiologist's Review # 1 of NDA 50-756
November 10, 1998

A. 1. APPLICATION NUMBER:

NDA 50-756

APPLICANT:

Dermik Laboratories
500 Arcola Road
Collegeville, PA 19426-0107

2. PRODUCT NAME:

Topical Gel

3. DOSAGE FORM: Clindamycin 1% and benzyl peroxide 5% gel packaged as two components : a polypropylene jar (benzoyl peroxide-containing gel) and polypropylene vial (clindamycin phosphate powder).

4. METHOD OF STERILIZATION: None (non-sterile product).

5. PHARMACOLOGICAL CATAGORY and/or PRINCIPLE INDICATION:

Antimicrobial indicated for the topical treatment of acne vulgaris. The applicant is not seeking an antimicrobial indication for the drug product.

B. 1. DATE OF INITIAL SUBMISSION:

April 9, 1998

2. DATE OF CONSULT:

June 16, 1998

3. RELATED DOCUMENTS:

(none)

4. ASSIGNED FOR REVIEW:

June 18, 1998

C. REMARKS: The consult request is for review of the microbial limit and preservative effectiveness testing for the drug product.

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Dermik Laboratories, NDA 50-756

Topical Gel

Microbiologist's Review #1

D. CONCLUSIONS:

The application is recommended for approval for issues concerning drug product microbial limits and preservative effectiveness testing. Specific comments are provided in section "E. REVIEW NOTES".

/S/ *11/10/98*
Neal Sweeney, Ph.D.
/S, 11/16/98

cc:

Original NDA 50-756
HFD-540/Division File
HFD-540/CSO/K.D.White
HFD-805/Consult File/N. Sweeney

Drafted by: Neal Sweeney, November 10, 1998
R/D initialed by P. Cooney, November 10, 1998

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DIVISION OF ANTI-INFECTIVE DRUG PRODUCTS
CLINICAL MICROBIOLOGY REVIEW
DERMATOLOGY CONSULT

JUN 22 1998

SUBMISSION TYPE: DOCUMENT DATE: CDER DATE: ASSIGNED DATE:
NDA 50-756 4/9/98 4/10/98 4/24/98

NAME AND ADDRESS OF APPLICANT:

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P.O. Box 1200
Collegeville, PA. 19426-0107
Phone: 610-454-8000

CONTACT PERSON:

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DRUG PRODUCT NAME:

Proprietary: _____ Topical Gel

Nonproprietary: None

Code Name/#'s: None

Chemical Formula: Clindamycin phosphate ($C_{18}H_{34}ClN_2O_8PS$) - See USP
Dictionary of USAN and International Drug Names 1997, pg. 173 for clindamycin
chemical structure + Benzoyl peroxide ($C_{14}H_{10}O_4$)- See USP Dictionary of USAN and
International Drug Names 1997, p. 87 for benzoyl peroxide chemical structure

INDICATIONS:

Topical Treatment of acne vulgaris

DOSAGE FORM: Topical gel

STRENGTH: Clindamycin phosphate 1% (10mg clindamycin phosphate/gram of gel) +
benzoyl peroxide 5% (50 mg benzoyl peroxide/gram) of gel.

ROUTE OF ADMINISTRATION: Topical

RELATED DOCUMENTS:

None

REMARKS/COMMENTS:

The applicant is not asking for an antibacterial claim for this product.

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Introduction

While the applicant is not asking for antibacterial claims they do indicate in their proposed package insert (vol. 1.1, pg. 1-59) that both of the ingredients in their product have antibacterial activity against *Propionibacterium acnes*. They further indicate that that a minimal inhibitory concentration (MIC) of 0.4µg/mL of clindamycin, as determined by in vitro testing inhibits all cultures of *P. acnes* tested. No indication is given as to the number of isolates tested or the source of the isolates. The applicant states (vol. 1.1, pg. 1-91) for the benzoyl peroxide ingredient of the product that the mean MIC for *P. acnes* is 200µg/mL but does not provide any further information such as a source of this information, method by which this information was derived, the number of isolates tested to determine this value, or literature references.

On page 1-90 (vol. 1.1) of the submission the applicant states under "Scientific Rationale" the following: "The rationale for the use of the clindamycin/benzoyl peroxide product in acne is based on the facts that both benzoyl peroxide and clindamycin are active against *P. acnes*, and benzoyl peroxide has keratolytic and desquamative activity." In support of the statement that clindamycin has activity against *P. acnes* the applicant cites a literature reference where it was shown in vitro that clindamycin exhibited an MIC of 0.125µg/mL versus 32 of 33 *P. acnes* isolates tested. The MIC of the one remaining isolate is not stated. Further references are cited which indicate in vivo activity against *P. acnes* which is thought to contribute to the pathogenesis of acne vulgaris. A literature reference is also given indicating that penetration of clindamycin into acne comedones has been reported to reach an average concentration of 0.824µg/mL.

The applicant (vol. 1.1, pg. 1-91) also cites a literature reference indicating that antimicrobial resistance is becoming an important factor in the treatment of acne. References are also cited which note an association between the presence of antibiotic resistant organisms and therapeutic failures. They also cite several references which indicate that the clinical use of topical clindamycin may result in clindamycin-resistant *P. acnes*. The applicant then goes on to cite references for the combination of 3% erythromycin/5% benzoyl peroxide (Benzamycin - approved by the FDA for treatment of acne vulgaris) and the fact that studies with Benzamycin demonstrate that increased antibacterial resistance can be avoided by the concomitant use of benzoyl peroxide with erythromycin. They extrapolate from this data that since clindamycin is a macrolide-like antibiotic that its combination with benzoyl peroxide could have an increased margin of safety in preventing the development of clindamycin-resistant and erythromycin-resistant organisms.

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Pre-Clinical Efficacy (in vitro):

Spectrum of Activity:

Clindamycin phosphate has been shown to have activity against *P. acnes* an anaerobic Gram-positive rod with the MIC₉₀ being approximately 0.25µg/mL (1). Benzoyl peroxide also has been reported to have activity against *P. acnes* (2).

Mechanism of Action:

Clindamycin inhibits the growth of bacteria by interfering with protein synthesis primarily in early chain elongation when the transpeptidation reaction occurs (3).

Benzoyl peroxide exerts its effect on bacteria through the liberation of oxygen as it is decomposed by cysteine in the skin. The liberated oxygen oxidizes the bacterial proteins causing death of the bacteria (4).

Mechanism(s) of resistance:

Bacteria may become resistant to clindamycin by alteration in a single 50s ribosomal protein of the receptor site or by alteration in the 23s ribosomal RNA of the 50s ribosomal subunit by methylation of adenine (3).

This reviewer was not able to find any well documented reports of bacteria resistant to the action of benzoyl peroxide.

Interaction with other Antibiotics:

Antagonism has been demonstrated in vitro between erythromycin and clindamycin. This antagonism is do to the fact that both antibiotics have the same site of action that being the 50s-ribosomal unit(5).

Pre-Clinical Information (in Vivo):

The applicant has indicated that an average concentration for clindamycin in comedones is 0.824µg/mg. This concentration is approximately 3x above the MIC₉₀ of *P. acnes* cited in the literature (1).

The concentration of benzoyl peroxide in comedones is not given by the applicant and a search of the literature did not reveal any well documented studies where the concentration of benzoyl peroxide in comedones was given.

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CONCLUSION:

This NDA submission lacks the applicant's own in vitro and in vivo microbiology data to substantiate the activity of the two components of _____ against what the applicant has stated is thought to be a cause of acne vulgaris namely *P. acnes*. While literature references are cited which provide MIC data for clindamycin against isolates of *P. acnes* these references are over 9 years old and may not reflect the MIC of *P. acnes* to clindamycin as it is today. No data or literature references are given for the MIC value stated for benzoyl peroxide against *P. acnes*. In addition, no data on the development of resistant organisms during the use of _____ is provided. This type of data could provide information on the efficacy of this product for the treatment of acne vulgaris over time. While extrapolation was made from information on the combination of benzoyl peroxide with erythromycin that the presence of benzoyl peroxide might provide a safety margin to the development of erythromycin-resistant organisms this type of data was not presented for the combination of clindamycin and benzoyl peroxide.

In respect to the microbiology aspect, the product is considered safe when used as indicated in the proposed package insert.

This NDA is approvable with the following changes made to the package insert.

Microbiology: The clindamycin and benzoyl peroxide components _____ have been shown to have in vitro activity against *Propionibacterium acnes* an organism which has been associated with acne vulgaris. The clinical significance of this activity against *P. acnes* _____ in clinical trials with this product.

PRECAUTION: Clindamycin and erythromycin containing products should not be used in combination _____

REFERENCES

1. Wise, R, and RC Ballard. 1989. Review of the evaluation of ECE 22101. J. Antimicrob. Chemother. 23:7-16.

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2. Tunkel, AR. Topical antibacterials. *In* Mandell, GL, Bennett, JH, Dolin, R, eds. Principles and Practice of Infectious Diseases, 4th ed. Churchill Livingstone, NY., 1995, 381-389.
3. Steibigel, NH. Macrolides and clindamycin. *In* Mandell, GL, Bennett, JH, Dolin, R, eds. Principles and Practice of infectious Diseases, 4th ed. Churchill Livingstone, NY., 1995, 334-346.
4. Fulton, JE Jr., A. Frazad-Backshandeh, and S. Bradley. 1974. J Cutan Pathol 1:191-200.
5. Eliopoulos, GM, and RC Moellering, Jr. Antimicrobial combinations. *In* Antibiotics in Laboratory Medicine, 4th ed. Williams & Wilkins, Baltimore, MD., 1996, 330-396.

[S 6/16/98]
Frederic J. Marsik, Ph.D.
Review Microbiologist

cc: Original 50-756
HFD-520 Divisional File
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HFD-540/CSO/K. White
HFD-520/Micro/F. Marsik

Concurrence Only
HFD-520/Dep/Dir/L. Gavrilovich

HFD-520/TLMicro/A.T. Sheldon
RD and Final 6/17/98 A.T.S.

[S S 6/22/98]

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